method, that allows the PMF to be extracted from nonequilibrium dynamics. In addition, the FR method allows the simultaneous determination of the reaction coordinate dependent diffusion coefficient, D(z). We recently extended the utility of the FR method through the use of an oscillating steering protocol that we named the oscillating forward-reverse (OFR) method. While working with OFR, the D(z) results did not match known values or those obtained through other methods. After reformulating the procedure to obtain D(z), we were able to obtain results close to the correct values. These results however showed very little variation over the length of the reaction coordinate, even when D(z) was known to vary drastically. It seemed that the highly variable and noncontinuous velocity function of the particle - a consequence of being steered using the ''stiff-spring'' method - was incompatible with the macroscopic definition of the drag coefficient through which D(z) is calculated. To address this, a new *dynamic constraint* steering protocol (DCP) was developed to replace the previously used ''stiff-spring'' method. We present here the results for D(z) in bulk water, and both the PMF and D(z) results from the permeation of a water molecule through a DPPC membrane. We also consider the issue of sufficient sampling, and propose that to obtain an accurate PMF (and D(z)) from even a moderately complex system, the final result should be a weighted average of numerous pulls. This is actually an advantage of nonequilibrium over equilibrium methods, the latter having a limited ability to sample much phase space beyond their initial conditions - especially with the time-scales currently available in computer simulations.

**110-Plat**
**A Multi Scale Approach for Path Sampling: Applications to Peptides**
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Path sampling techniques are a versatile tool to probe rare events in complex dynamics, but the conventional methods are often limited to rare but fast processes such as chemical reactions (~ps). Here we are interested in much slower processes such as conformational transitions or folding of proteins, and the direct application of the conventional methods can fail for such a situation. We have been pursuing alternative path sampling methods based on the Onsager-Machlup (OM) action functional for diffusive processes. We showed that the OM action method can be combined with replica exchange for effective path sampling (H. Fujisaki et al., J. Chem. Phys. **132**, 134101 (2010)) and proposed to combine it with the multi-scale essential sampling method (K. Moritsugu et al., J. Chem. Phys. **133**, 224105 (2010)) for larger molecular systems. In this presentation we employ the model polymer system (C. Micheletti et al., J. Chem. Phys. **129**, 074105 (2008)), and numerically show the effectiveness of our new method. We also apply our method to some peptide systems, and discuss the success and limitations of the method.

**111-Plat**
**Decoding Hidden Complexities of Kinetic Experiments**
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Time trace data obtained from single-molecule kinetic experiments such as fluorescence, ion conduction and force extension, often appear in the form of stochastic time trajectories, exhibiting complex behavior that cannot be described by a single exponential. The underlying system is usually modeled as aggregated Markov states, where each experimentally observable property comes from an aggregate of indistinguishable states, making transitions to each other via Markov process. However, such a modeling has limitations in that the underlying network topology has to be assumed in advance, and that there are many models consistent with the data. In this work, we introduce a new method of modeling such systems using a non-Markov model. In contrast to the aggregated Markov model, the new method leads to a unique dynamical model for a given time trace data. Furthermore, it is shown that the current formalism is more general than the aggregated Markov model, including the latter as a special case. We also develop an algorithm for extracting the non-Markov memory kernel from a noisy experimental data, based on the Maximum Entropy Principle, the method for the unbiased estimation. Some preliminary analysis of simulated and real experimental data will be presented.

**112-Plat**
**Computational Electrophysiology Reveals Ion Channel Permeation in Atomistic Detail**
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Presently, simulations of ion channel permeation usually rely on nonatomistic Brownian dynamics calculations, indirect interpretation of energy maps or external electric fields. In biological cells, however, electric fields across bilayers are generally established by electrochemical ionic gradients. Small charge imbalances across the bilayers also evoke electric fields applied in electrophysiological experiments on a microscopic scale.
We present a computational method which enables the direct simulation of ion flux through membrane channels driven by biologically realistic electrochemical gradients. This also makes the simulation of reversal potential experiments possible. As it is implemented in a highly efficient molecular dynamics package, simulation timescales relevant for physiology and experiment, for instance single-channel electrophysiology, are achieved.
We illustrate the use of our method by applying it to the bacterial channel PorB from pathogenic Neisseria meningitidis. PorB inserts into the inner mitochondrial membrane of target cells during Neisserial infection and triggers their apoptosis by dissipating the potential across the membrane. These channels must also be passable for antibiotics during treatment. We show that the method accurately predicts ion conductance and selectivity and elucidates detailed ion conduction mechanisms. PorB mutants resistant to antibiotics display a markedly altered ion pathway and selectivity.

**113-Plat**
**Multi-Network Modeling of Cancer Cell States**
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Cellular signaling networks involved in cancer are highly interconnected. Including molecular details into a model presents a serious challenge, because of the limited information on specific interactions. At the same time, clinicians accumulate a great deal of data about expression of some proteins (such as EGFR, mTOR, Erk1) in different cancer types, and effects of mutations and drug treatments on protein expressions. Each of these proteins is known to be a key regulator for certain signaling networks leading to different cell fates. Different cancer types can be distinguished by concentrations of these key proteins and by different combinations and temporal patterns of five cell states (senescense, proliferation, quiescence, death or stemness). We use experimental data from different cancer types to create a predictive kinetic model of cell states. The model consists of five signaling modules (Ras, Akt, Myc, Notch and Wnt) and a single cell fate module. Each signaling module describes parts of signaling networks known to influence cell state. Each module has several molecular inputs - measurable quantities like EGFR concentration - and several molecular outputs - predicted quantities like Ras concentration. Molecular outputs of signaling modules are integrated to affect transitions among cell states in the cell fate module, while the given cell state determines inputs for all signaling modules. The model is able to account for perturbations, including mutations and drug treatments. Our approach is a step toward a simplified, personalized compendium of the most critical information for predicting cancer patient's response to a targeted therapeutic.

**114-Plat**
**Analysis of Collective Coevolution in HIV Proteins Suggests Strategies for Rational Vaccine Design**
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The rapid evolution of HIV in sequence space evades adaptive immune responses (T cells and neutralizing antibodies) and has posed significant challenges in the design of protective vaccines. We hypothesized that characterizing collective correlations between different amino acid mutations within HIV proteins would reveal proteomic regions that evolve independently from